The frequency of inappropriate non-formulary medication alert overrides in the inpatient setting

Keywords: formulary, clinical decision support, alerts, computerized provider order entry, appropriateness, information system

Abstract

Background: Experts suggests formulary alerts at medication order entry is the most effective form of clinical decision support to automating formulary management.

Objective: Our objectives was to quantifying the frequency of inappropriate NFM alert overrides in the inpatient setting and provide insight on how to better design formulary alerts for automated formulary management.

Methods: The NFM alert overrides of 206 highest costing and most utilized NFM from 2012 were randomly selected for appropriateness evaluation. Using an empirically developed NFM alert appropriateness algorithm, appropriateness of NFM alert overrides were assess by two pharmacist via in-depth chart review. Appropriateness agreement of NFM alert overrides was assessed with a Cohen's kappa. Exploratory analysis assessed which types of NFMs were most likely to be inappropriately overridden, which type of override reasons was disproportionately associated with inappropriate alert overrides, and what reasons explained why a NFM alert was overridden inappropriate.

Results: Approximately 17.5% (n=36/206) of NFM alerts are inappropriately overridden. Non-oral NFMs alerts are more likely to be inappropriately overridden compared to oral NFMs. Alerts overridden with 'blank' reasons were more likely to be inappropriate. The failure to first trial a formulary alternative is the most common reason for a NFM alert overridden inappropriately.

Conclusion: Conservatively about one in five NFM alert overrides are overridden inappropriately. Mandating an override reason for each NFM alert override and adding a list of

formulary alternatives to each NFM alert may decrease the frequency of inappropriate NFM alert overrides.

Introduction

A hospital formulary is a list of medications agreed upon by hospital healthcare providers for the care of admitted patients.[1] Medications on this list are often the cost-effective option compared to their non-formulary alternatives, also termed non-formulary medications (NFMs). Typically, NFMs are not stocked and require special order entry and procurement procedures by the prescriber and pharmacy prior to use. These special order entry and procurement procedures increases labor cost ($15.94 to $23.34)[2-4] and can substantially delay NFM initiation (10.6 hours).[3] NFMs are also error prone, because they are unfamiliar to hospital staff may be misinterpret for the more familiar formulary medications.[5-8]

However, the need for hospitals to provide NFMs is inevitable. There are times when admitted patients are stabilized on a pre-admission, chronic NFM and substitution with a formulary alternative can induce harm. Experts suggests formulary CDS, at medication order entry, in the form of a pop-up alert containing a list of formulary alternatives is the most effective design in balancing the need of NFMs while limiting the ill-effects of formulary non-compliance.[9] Empiric verification of this suggestion is limited. Analogous evidence can be drawn from the more commonly used computerized alerts (drug-allergy, drug-drug interactions, drug-disease contraindication, etc.), where studies have shown these alerts improve prescribing behaviors, reduce prescribing errors, impact clinical outcomes, and decrease medication cost.[10] However, these benefits have often been challenged by the high frequency of alert overrides (49-96%).[11] Therefore, we are unsure if the aforementioned alerts benefits can be generalized to formulary alerts.

To our knowledge there are no studies evaluating the appropriateness of NFM alert overrides. Our experience suggests this may be attributed to the resource-intensive task of creating appropriateness criteria for each NFM. In our previous study, we empirically developed a 'general' appropriateness algorithm that institutions could adapted to evaluate the appropriateness of their institution specific NFM alert overrides. We adapted this general algorithm to our institution's NFM use policy and criteria and evaluated the appropriateness of a random sample of NFM alert overrides.

Methods

Setting

Brigham and Women's Hospital (BWH) is a 793-bed academic medical center located in Boston, MA and admits approximately 46,000 patients annually for a full range of inpatient services, with the exception of pediatrics. Medications available for patient care are governed by BWH's formulary. Inpatient medications are ordered through an in-housed developed computerized provider order entry (CPOE) system inside Brigham Integrated Computer System (BICS). Full details of BICSand the CPOE system are described elsewhere.[12] Formulary alerts embedded in the CPOE system are used to automate formulary management. Upon order entry of a NFM, prescribers are informed of its non-formulary status with three types of pop-up alerts: 1) a 'soft stop' requesting the input of a free-texted override reasons, explaining the rationale of formulary deviation, 2) an 'intermediate stop' requesting an override reason and the identifying the specialist physician who approved the NFM for use, and 3) a 'hard stop'

stating the NFM is not available for use and prompting the prescriber to order the preferred formulary alternative **(Figure 1 and 2)**.

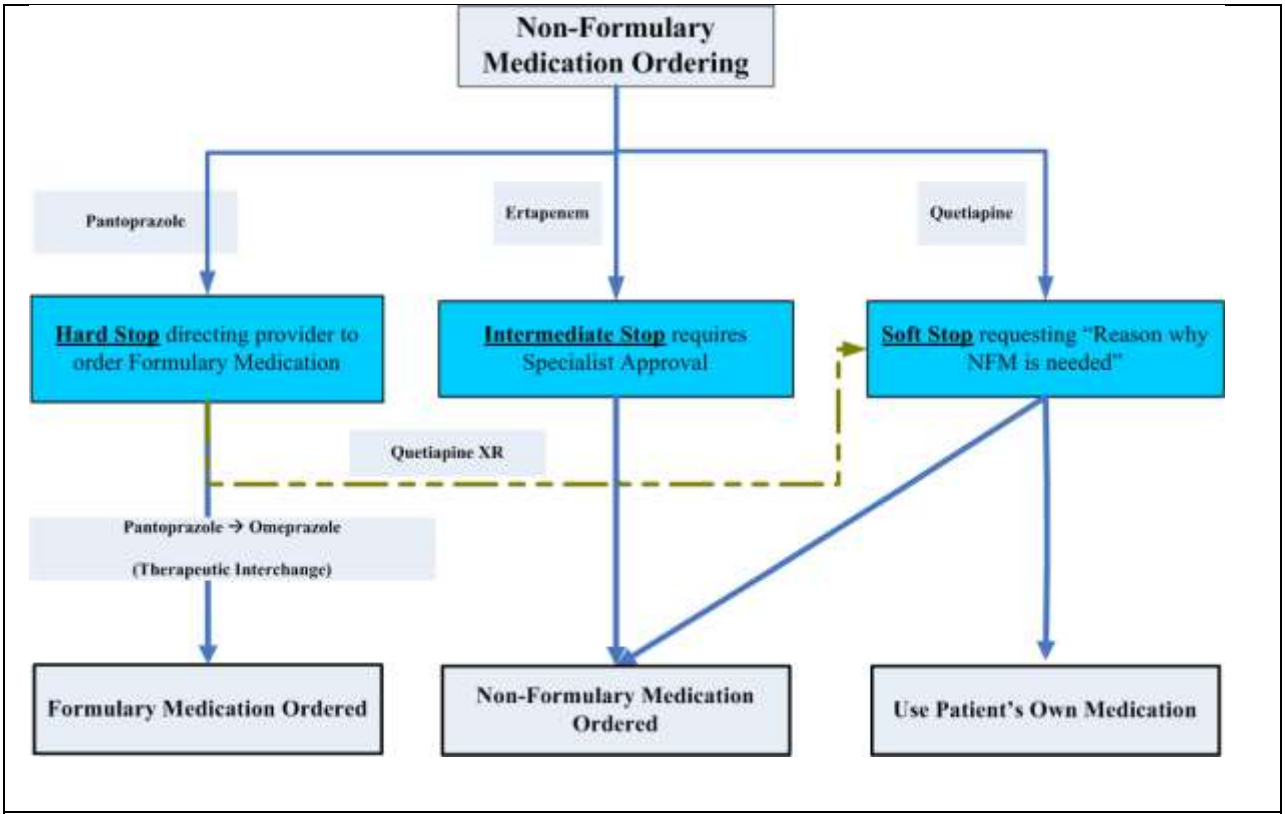
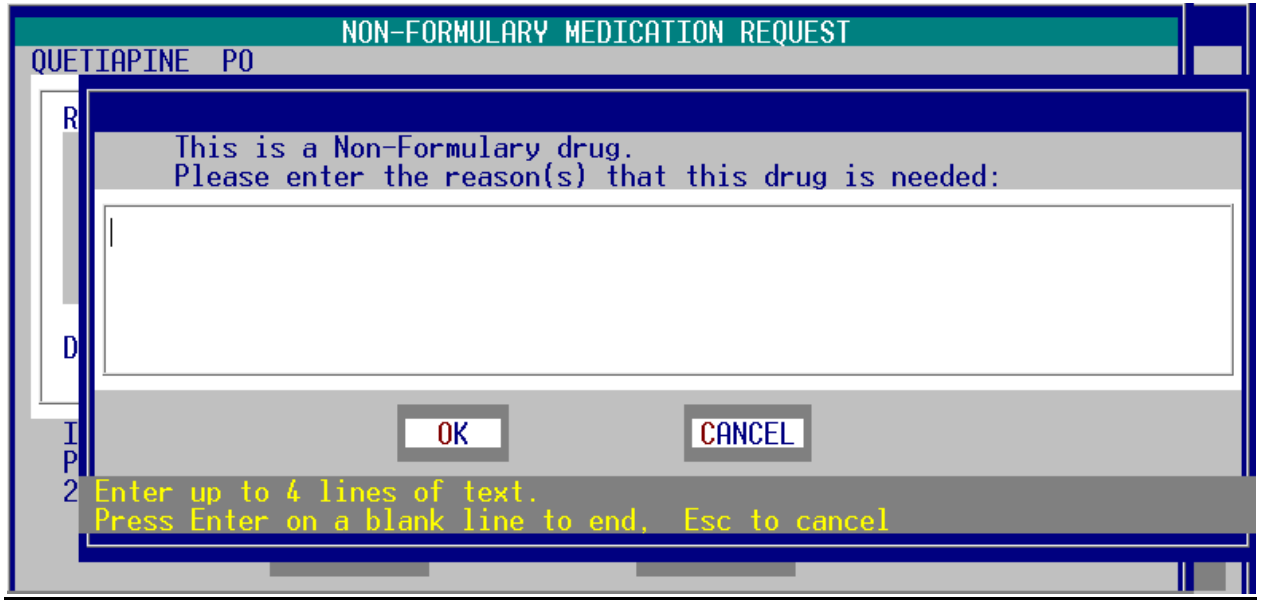


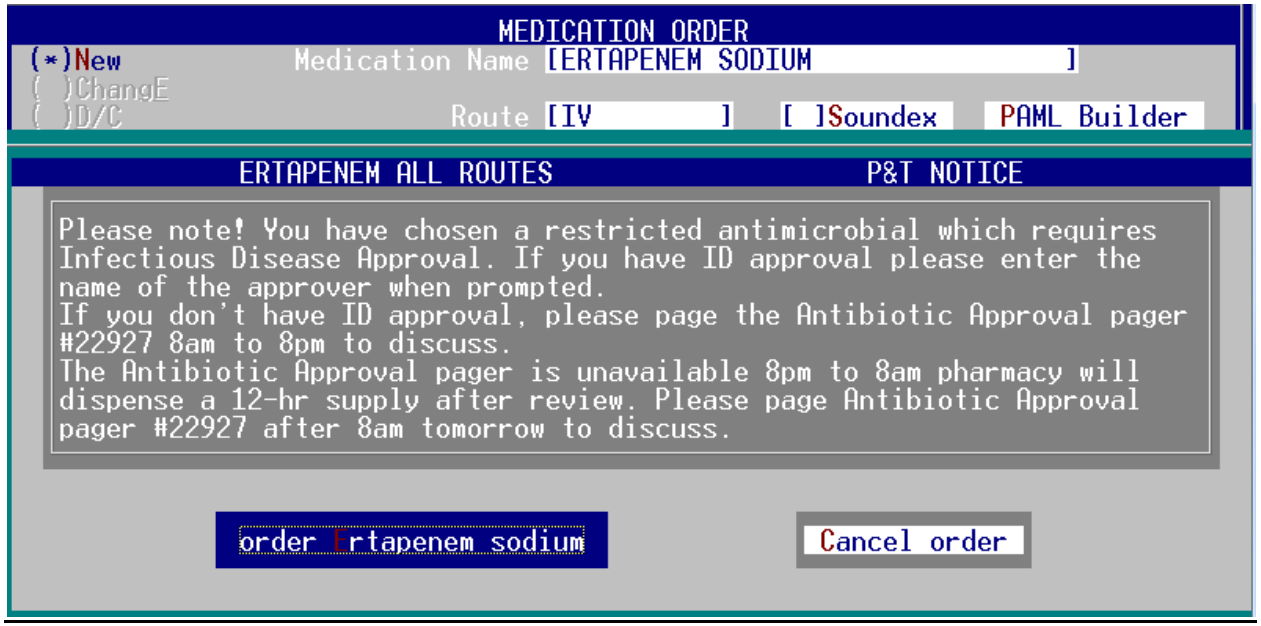
Figure 1: Non-formulary medication alerts

The dashed line represents the hard stop directing the prescriber to order a preferred NFM alternative. In this example Quetiapine XR cannot be ordered, but the hard stop directs the prescriber to order Quetiapine which is also NFM. The soft stop directs the provider to enter a reason why NFM is needed.

A.


NON-FORMULARY MEDICATION REQUEST
QUETIAPINE PO
This is a Non-Formulary drug.
Please enter the reason(s) that this drug is needed:
OK
CANCEL
Enter up to 4 lines of text.
Press Enter on a blank line to end, Esc to cancel

B.


MEDICATION ORDER
(*)New
Medication Name [ERTAPENEM SODIUM]
( )ChangE
( )D/C
Route [IV] [ ]Soundex PAML Builder
ERTAPENEM ALL ROUTES P&T NOTICE
Please note! You have chosen a restricted antimicrobial which requires Infectious Disease Approval. If you have ID approval please enter the name of the approver when prompted.
If you don't have ID approval, please page the Antibiotic Approval pager #22927 8am to 8pm to discuss.
The Antibiotic Approval pager is unavailable 8pm to 8am pharmacy will dispense a 12-hr supply after review. Please page Antibiotic Approval pager #22927 after 8am tomorrow to discuss.
order Ertapenem sodium
Cancel order

C.

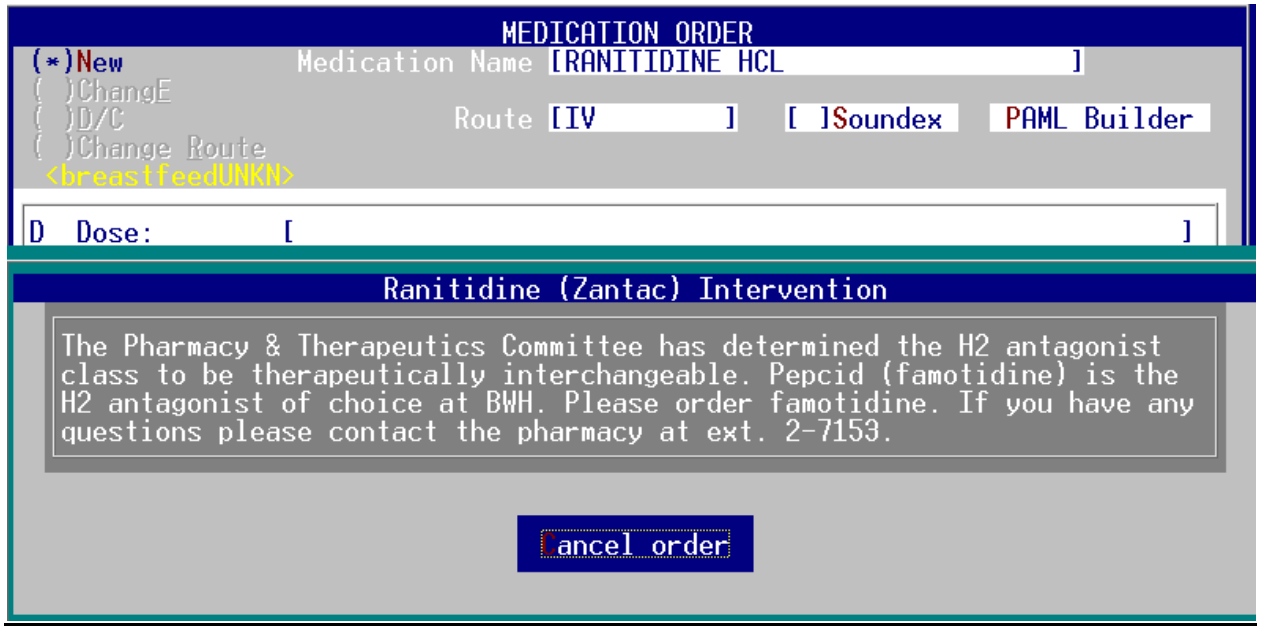


Figure 2: Non-formulary pop-up alerts

A) Soft stop, B) Intermediate stop, and C) Hard stop

Study Design and Sampling of NFM alert overrides

The present study was an observational study of NFM alerts overridden from January 1st to December 31st, 2012. These overrides and their relevant data elements were extracted from BICS and loaded into a Microsoft Access Database (Microsoft Corp, Redmond, WA). Relevant data elements included patient's medical record number, patient name, admission date, discharge date, NFM order entry date, NFM order entry time, medication unique identifier, generic medication name, route, dosage, dosing frequency, estimated number of doses required, , prescriber name, prescriber unique identifier, and the free-texted NFM alert override reason.

We limited our sample of NFM alert overrides to only original overrides and excluded those that were the result of medication dose, direction, or frequency changes. The latter overrides' rational for formulary deviation were often the same as the original and including them into our evaluation would duplicate alerts. Further, at BWH there are two sources of non-formulary designation, one in BICS and the other in an online formulary dictionary. Our internal study found inconsistencies in these two sources. To ensure our evaluation included only true NFMs, we further limited our overrides sample to medications listed as non-formulary in both sources.

Total medication cost, composed of procurement and medication cost from 2009 to 2012, were computed for each NFM. The average procurement cost of providing a NFM over formulary alternatives was estimated to be $20.07 per order.[2] This estimate was used to convert the number of NFM orders to a monetary value. Medication costs were estimated from a BWH's medication wholesaler account during the first quarter of 2014. NFMs were ranked

from highest to lowest total cost and twenty alert overrides were randomly selected from the top 11 NFMs for alert override appropriateness evaluation. **Figure 3** describes our NFM alert override sampling scheme.

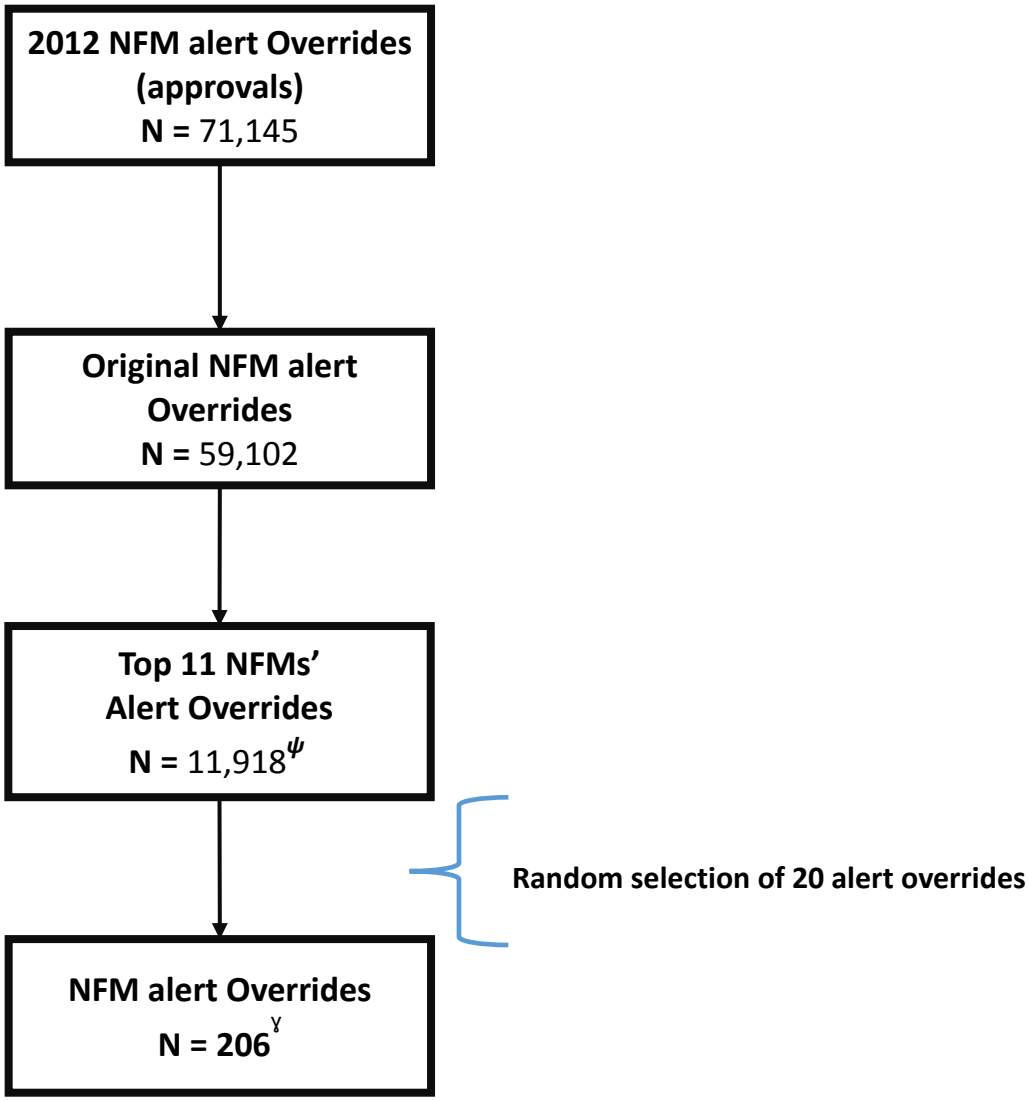


Figure 3: NFM alert override random selection
ψTop 11 most approved and highest costing NFMs
ɣIn 2012 there were only six alert overrides for liposomal doxorubicin

NFM alert override appropriateness criteria

Previously, we empirically developed a general NFM alert override appropriateness algorithm from free-texted NFM alert override reasons. Full details of the methodology and performance of the algorithm can be found elsewhere *(citation AJHP Study)*. In brief, a NFM alert override reason categorization scheme was created from a random sample of 5,000 overrides according to keywords, context, and value explaining the rationale for formulary deviation. A 30 question appropriateness algorithm was initially developed from these override reason categories and presented to an interdisciplinary team of healthcare providers to evaluate clinical creditability and for feedback. BWH inpatient pharmacist and pharmacy administrators were also consulted on the NFM ordering process and the algorithm was simplified to an eight question general appropriateness algorithm **(Figure 4)**. Available BWH medication monographs, treatment guidelines and medication administration guidelines of the top 11 NFMs were ascertained from the BWH Pharmacy intranet website and incorporated into the general algorithm to create insitution specific NFM alert override algorithms.

Figure 4: General NFM alert override appropriateness algorithm

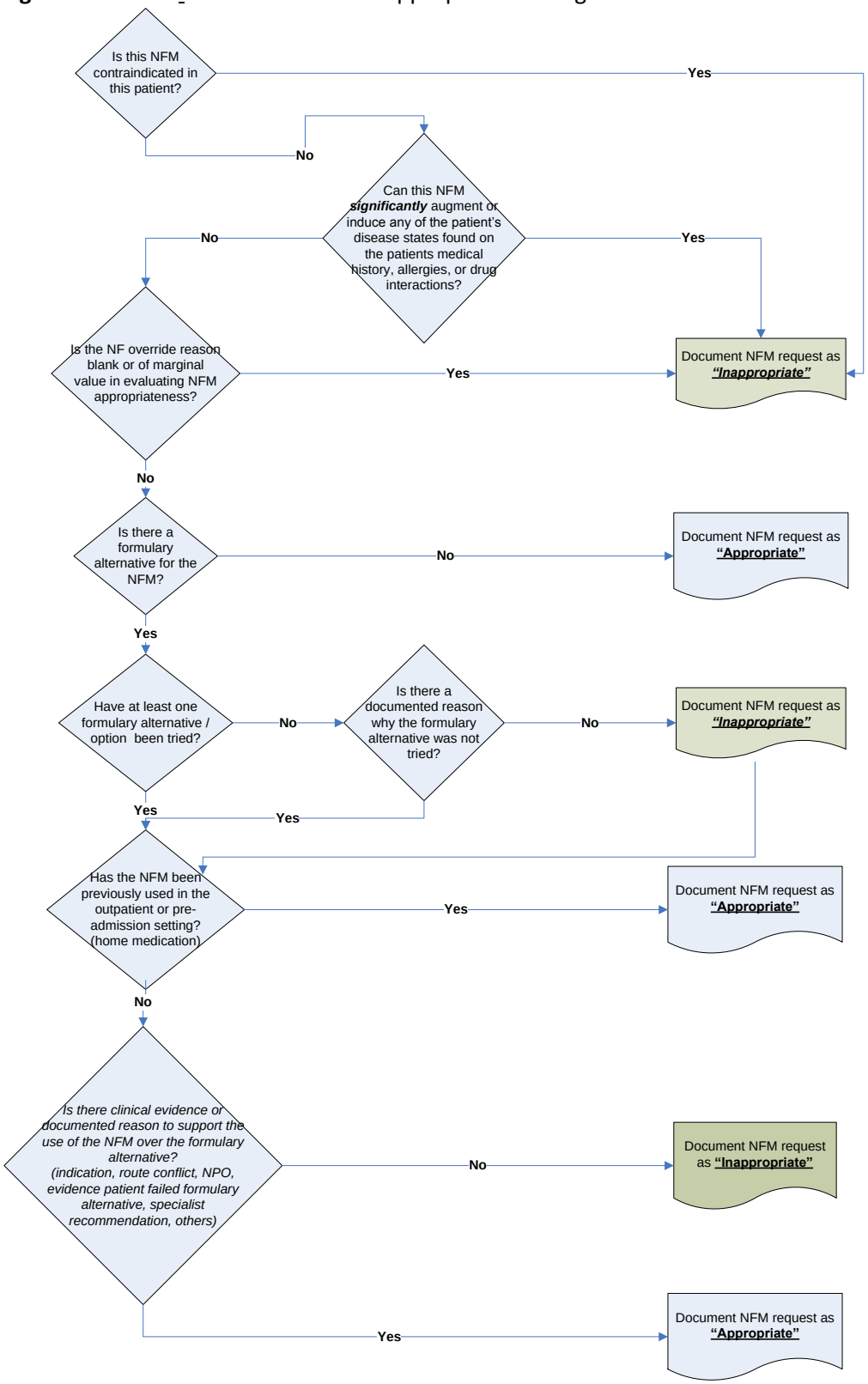


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Chart review and appropriateness evaluation

An appropriateness evaluation interface was created in a Microsoft Access Form, where all aforementioned relevant data elements were displayed. This was an attempt to mimic formulary management at the at the point of care. All inpatient notes in "portable document format" (PDF) corresponding to the hospitalization when the NFM alert was overridden was downloaded from BICS and a hyperlink to this document was created in the Microsoft Access Form to facilitate reviewer access. All medication orders, labs, and medication administration logs during hospitalization were available through BICS. Outpatient medication records were available through BWH's ambulatory care electronic medical record, Longitudinal Medical Record (LMR).

Two pharmacists (QLH and MGA) assess the appropriateness of each NFM alert override according to the institution specific NFM appropriateness algorithms via in-depth chart. Generally, pharmacists first reviewed the override reason explaining the formulary deviation and identified 'preliminary' formulary alternatives to the NFM. Second, the pharmacists ensured that the NFM was not contraindicated or potentially induced any significant harm to the patient according to the information found in the inpatient chart (i.e. chief complaint of admission, medical history, allergies, or drug interactions). If the NFM posed any threat of harming the patient, the NFM alert override was considered inappropriate. The reviewers also reviewed medication orders and medication administration logs for evidence of trialing formulary alternatives prior to the NFM alert override. The NFM alert override was considered appropriate if a formulary alternative was first tried or documentation in the inpatient notes reasonably explained why a formulary alternative was not an option, otherwise the NFM alert

override was inappropriate. Disagreements between pharmacists were resolved by discussion with a third reviewer (DLS).

In our previous study, approximately one-half of all NFM alerts overrides were justified with entered blanks and marginal value reasons (i.e. patient needs medication, patient requires, attending prefers, etc.) ***(AJHP citation)***. It is possible that these overrides are appropriate, but justification was poorly documented. For example, there could be occasions where specialist were consulted or formulary alternatives were thoroughly evaluated and found to induced drug interactions, but the prescriber passively entered a 'blank' or marginal value reason in the NFM alert override interface. Thus, 'blank' and marginal value reasons were deemed inappropriate unless an appropriate justification (specialist consult, pharmacological interaction, active disease that required the medication etc) for the NFM was discovered during chart review.

Our previous study, we also found a significant number of NFM alert overrides were justified with syntax variants of the NFM being a pre-admission or home medication. In these cases the NFM alert override was considered appropriate only if the NFM was found active in the LMR's electronic medication list during the dates of hospitalization. For NFMs justified by a 'disease or condition' reason, the literature was searched to ensure minimal supporting evidence existed (at least a case-report) for the NFM's proposed indication. Any level of clinical evidence found concluding effectiveness and citation of the 'disease or condition' in the inpatient notes prompted these overrides to be deemed as appropriate. Remaining potential reasons included specialist or pharmacist recommendation, therapeutic failure or intolerance to NFMs, pharmacological reasons, end of life care, and drug shortages. NFM alerts overridden

with these reasons were appropriate as long as there was documented evidence in the inpatient notes. For example, olanzapine was often justified with 'per psych recommendation,' this NFM alert override would be considered appropriate if a psychiatrist consult recommending the medication was existed in the inpatient notes prior the NFM being ordered.

Outcomes and objectives

Our primary objective was to quantify the frequency of NFM alerts overridden inappropriately, computed as the ratio of NFM alerts overridden not according to our appropriateness algorithms over the total number of overrides in our sample. Secondary objectives included identifiying (1) which types of NFMs (oral and non-oral) were most likely to be inappropriately overridden, (2) which category of NFM alert override reasons disproportionately represent inappropriate NFM alert overrides, and (3) reasons explaining why the NFM alert override was inappropriate. ***A post-hoc analysis was report the frequency of override reason given in NFM alert pop-up not congruent to the formulary deviation reason documented in the inpatient notes; we term these discrepancies as discordant override reasons.***

Statistical Analysis

Counts and frequencies were used to summarize the number of inappropriate overrides according to our NFM alert override reason categorization scheme. Agreement in the inappropriateness of NFM alert overrides between the two pharmacists was evaluated with a Cohen's kappa. Fischer's exact test was used to compare the distribution of inappropriate NFM

178 alert overrides among oral and non-oral NFMs. A p-value of less than 0.05 was considered to be
179 statistically significant.

180 A Fischer's exact test was also first used to determine if inappropriate NFM alert
181 overrides were disproportionately distributed among the override reasons categories. ***If the***
182 ***exact test was found to be statistical significant (p-value < 0.05), the frequency of***
183 ***inappropriate overrides in each override reason category was compared to the frequency of***
184 ***the override reasons using a student t-test. A Bonferroni correction was applied to the student***
185 ***t-test to adjust for multiple testing.*** All statistical analyses were conducted using SAS software
186 (version 9.4 SAS Institute, Cary, NC). This study was approved by the Partners Human Research
187 Committee.

Results

Table 1

Top 11 Most Approved and Highest Costing NFMs	Number of NFM Alert Overrides	Inappropriate Alert Overrides	Frequency of Inappropriate Alert Override	Percentage of Total Inappropriate Alert Overrides
Oral non-formulary medications (n=80, 38.8%)				
Aprepitant (PO)	20	0	0.0%	13.9%
Olanzapine (PO)	20	0	0.0%	
Olanzapine ODT (PO)	20	1	5.0%	
Quetiapine (PO)	20	4	20.0%	
Non-oral non-formulary medications (n= 126, 61.2%)				
Dornase Alfa (Neb)	20	4	20.0%	86.1%
Liposomal Doxorubicin (IV)	6	0	0.0%	
Metronidazole 1% (Cream)	20	6	30.0%	
Mometasone Furoate (Inhaler)	20	4	20.0%	
Ranitidine (IV)	20	16	80.0%	
Rasburicase (IV)	20	0	0.0%	
Scopolamine (Patch)	20	1	5.0%	
Total	206	36	17.5%	100.0%

In 2012, 71,145 NFM alerts were overridden, of which 59,102 were original alert overrides for 45,352 hospitalizations. Thus, about 1.3 original NFM alerts were overridden with each hospitalization. The top 11 most approved and highest costing NFMs can be found in **Table 1**. Four NFMs were oral medications, of which three were atypical antipsychotics. The remaining seven included three intravenous medications, two inhalants, and two topicals. The random selection scheme selected 206 NFM alerts overrides from these medications (there were only six liposomal doxorubicin orders in 2012), which were prescribed by 174 distinct health care providers: 150 physicians, 21 physician-assistants, and three pharmacists.

198 According to the appropriateness algorithms, the two pharmacists found 36 (17.5%)
199 NFM alerts inappropriately overridden **(Table 1)**. Agreement between reviewers was high,
200 κ=0.97 (95% CI: 0.92 – 1.00). Inappropriate alert overrides were disproportionately nested in
201 non-oral NFMs (p=0.007), where 86.1% (n=31) of inappropriate alert overrides were from non-
202 oral NFMs, while they constituted only 61.2% of the alert override sample **(Table 1)**.

Table 2: Non-Formulary Medication Alert Override Appropriateness Evaluation

Initiate Non-Formulary Override Reason Classification	Total Number (Percentage of Total)	Final Appropriateness Evaluation		
		Appropriate	Inappropriate (Percentage of Total)	P-Value[1]
Blank	**51 (24.8%)**	**31**	**20 (55.6%)**	***0.0001***
Disease or Condition Listed	**64 (31.1%)**	**60**	**4 (11.1%)**	***0.0004***
Home or Pre-Admission Medication	**38 (18.4%)**	**33**	**5 (13.9%)**	**0.4401**
Marginal Value for NF Decision:	**30 (14.6%)**	**26**	**4 (11.1%)**	**0.5204**
Acknowledge NF status	2 (1%)	2	0 (0%)	
Content Free	1 (0.5%)	1	0 (0%)	
MD/Attending/Team Request, Prefers NF Medication	11 (5.3%)	8	3 (8.3%)	
MisCommunication: Medication use direction	3 (1.5%)	3	0 (0%)	
Others	2 (1%)	2	0 (0%)	
Patient Preference/Request	2 (1%)	2	0 (0%)	
Reason Listed "Appropriate, Effective, Indicated, Medical Necessity, No Alternative	1 (0.5%)	1	0 (0%)	
Reason Listed "Need/Requir* OR Patient Need*/Require**	8 (3.9%)	7	1 (2.8%)	
Pharmacological Reason:	**4 (1.9%)**	**3**	**1 (2.8%)**	**0.6908**
Contraindication	1 (0.5%)	1	0 (0%)	
Drug Route Conflict	1 (0.5%)	0	1 (2.8%)	
Others	2 (1%)	2	0 (0%)	
Specialist Recommendation	**10 (4.9%)**	**9**	**1 (2.8%)**	**0.4442**
Therapeutic Failure / Intolerant to formulary alternatives:	**9 (4.4%)**	**8**	**1 (2.8%)**	**0.6092**
Medication Listed	6 (2.9%)	6	0 (0%)	
Unspecified or Medication Not Listed	3 (1.5%)	2	1 (2.8%)	

Total	**206**	**170**	**36**	

[1]***P-values less than 0.007 (=0.05/7) were considered statistically significant, after application of a Bonferroni correction.***

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There were 117 unique override reasons in the 206 NFM alert override sample. These reasons were categorized into 17 of the 24 previously developed override reason categories **(Table 2)**. The most common reason explaining formulary deviation was the provision of a 'disease or condition' (31.1%, n=64). No ('blank,' n=51) or marginal value reasons (n=30) were provided in 39.4% of the alert override sample. 'Home or Pre-Admission Medications' reasons were used to justify for 18.4% (n=38) and clinical reasons of pharmacological, specialist recommendation, and failure or intolerance to formulary alternatives definition for only 11.2% (n=23) of the NFM alert override sample.

Fischer's exact test confirmed a disproportionate distribution of inappropriate overrides among the categories of override reasonsin our sample of alert overrides, $p< 0.001$. Specifically, subanalysis found 55.6% (n=20) of inappropriate overrides were nested in the 'blank' override reason category, while 'blanks' only accounted for 24.8% of all override reasons, $p=0.0001$. Contrary, 11.1% of inappropriate overrides were nested in the 'disease or condition' reason category, while these reasons accounted for 31.1% of the reasons in our sample, $p=0.0004$. Statistical analysis did not find a disproportionate number of inappropriate overrides in the remaining override reason categories **(Table 2)**.

Chart reviews identified 24 (66.7%) of the 36 inappropriate NFM alert overrides were the result of not trialing formulary alternatives prior to the NFM **(Table 3)**. Eight (22.2%) of the inappropriate NFM alert overrides were justified as a pre-admission or home medication, but no evidence of active outpatient prescription was found in the patient's LMR. Chart reviews also found no or limited information justifying the use of the NFMs in three (8.3%) inappropriate overrides. These overrides were overridden with a 'blank' or marginal value

reason (prescriber preference). Lastly, there was one case where the NFM was deemed clinically inappropriate to the patient involving the use of an atypical antipsychotic to address dementia in an elderly patient, which has been linked to adverse outcome in chronic and as-needed used.[13,14] Post-hoc analysis identified found 'blank' and marginal value reasons have the highest frequency of discordant override reasons, 94.1% and 93.3%, respectively **(Table 4)**.

Table 3: Reasons explaining why the NFM alert override was considered inappropriate

Non-Formulary Alert Override Reason Class	Total	Formulary alternative was not first trial prior to NFM alert override	No citation or information could be found justifying formulary deviation during chart review	Clinically Inappropriate	No evidence of active home medication found in LMR	No documentation of specialist recommendation during chart review
Blank	**20**	**17**	**1**	0	**2**	0
Disease or Condition Listed	**4**	**4**	0	0	0	0
Home or Pre-Admission Medication	**5**	0	0	0	**5**	0
Marginal Value for NF Decision: MD/Attending/Team Request, Prefers NF Medication	**3**	0	**2**	**1**	0	0
Marginal Value for NF Decision: Reason Listed "Need*/Requir* OR Patient Need*/Require*	**1**	0	0	0	**1**	0
Pharmacological Reason: Drug Route Conflict	**1**	0	0	0	0	**1**
Specialist Recommendation	**1**	**1**	0	0	0	0
Therapeutic Failure / Intolerant to formulary alternatives: [Unspecified or Medication Not Listed]	**1**	**1**	0	0	0	0
Total	**36**	**23 (63.89%)**	**3 (8.33%)**	**1 (2.78%)**	**8 (22.22%)**	**1 (2.78%)**

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Table 4: Frequency of Discordant NFM Alert Override Reasons

Initiate Non-Formulary Override Reason Classification	Final NFM Override Reason Category (Post-Chart Review)									
	Total	**Frequency of Discordant Reason for NFM Alert Override**	**Blank**	**Disease or Condition Listed**	**Home or Pre-Admission Medication**	**Marginal Value for NF Decision:** *MD/Attending/Team Request, Prefers, NF Medication*	**Pharmacological Reason:** *Drug Route Conflict*	**Pharmacological Reason:** *Others*	**Specialist Recommendation**	**Therapeutic Failure / Intolerant to formulary alternatives:** *[Medication Listed]*
Blank	**51**	**94.1%**	**3**	**42**	**3**	**0**	**0**	**0**	**0**	**3**
Disease or Condition Listed	**64**	**7.8%**	**0**	**59**	**4**	**0**	**1**	**0**	**0**	**0**
Home or Pre-Admission Medication	**38**	**10.5%**	**0**	**1**	**34**	**0**	**0**	**0**	**3**	**0**
Marginal Value for NF Decision:	**30**	**93.3%**	**0**	**16**	**10**	**2**	**1**	**0**	**0**	**1**
MisCommunication: Medication use direction	3	100.0%	0	2	1	0	0	0	0	0
Acknowledge NF status	2	100.0%	0	1	1	0	0	0	0	0
Content Free	1	100.0%	0	1	0	0	0	0	0	0
MD/Attending/Team Request, Prefers NF Medication	11	81.8%	0	7	2	2	0	0	0	0
Others	2	100.0%	0	2	0	0	0	0	0	0
Patient Preference/Request	2	100.0%	0	0	1	0	1	0	0	0
Reason Listed "Appropriate, Effective, Indicated, Medical Necessity, No Alternative	1	100.0%	0	0	0	0	0	0	0	1
Reason Listed "Need/Requir* OR Patient Need*/Require**	8	100.0%	0	3	5	0	0	0	0	0
Pharmacological Reason:	**4**	**50.0%**	**0**	**1**	**0**	**0**	**1**	**1**	**0**	**1**
Contraindication	1	100.0%	0	1	0	0	0	0	0	0
Drug Route Conflict	1	0.0%	0	0	0	0	1	0	0	0
Others	2	50.0%	0	0	0	0	0	1	0	1
Specialist Recommendation: Specialist / Other Service Recommended	**10**	**20.0%**	**0**	**2**	**0**	**0**	**0**	**0**	**8**	**0**

Therapeutic Failure / Intolerant to formulary alternatives:	**9**	**33.3%**	**0**	**1**	**0**	**0**	**0**	**0**	**0**	**8**
Medication Listed	6	0.0%	0	0	0	0	0	0	0	6
Unspecified or Medication Not Listed	3	33.3%	0	1	0	0	0	0	0	2
Total	**206**		**3**	**122**	**51**	**2**	**3**	**1**	**11**	**13**

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Discussion

Our observational study found approximately one-fifth of NFM alerts at our institution are inappropriately overridden. Non-oral NFMs alerts were more likely to be inappropriately overridden compared to oral NFMs. We also found NFM alerts overridden with 'blank' were more likely to be inappropriately overridden. Contrary, alerts overridden with 'disease or condition' reasons are less likely to be inappropriately overridden. In-depth chart review found the failure to trial a formulary alternative is the most common reason for a NFM alert override to be inappropriate. Lastly, NFM alerts overridden with 'blank' or 'marginal value' reasons often had justifiable formulary deviation reasons in the medical notes, but poorly documented in the NFM alert pop-up interface.

To our knowledge there are no studies evaluating the appropriateness of NFM alert overrides. This is likely attributed to the resource-intensive task of creating appropriateness criteria for each NFM. Thus, we are unsure of how our findings compared to other institutions. However, evaluating NFM alerts is inherently evaluating NFM use. Therefore, inappropriate NFM usage frequencies may provide some estimation of the frequency of inappropriate NFM alerts overrides.

Available studies suggest the frequency of inappropriate NFM usage is approximately 60% to 70%. Specifically, a small 6-week prospective study at an academic medical center found 61% of NFM use failed to comply to institution criteria[8] and a study evaluating the impact of a comprehensive formulary management system from a no structured system decreased NFM utilization from 17.8 to 5.9 medications per 100 admissions. This suggests an upper 67% bound

of inappropriate NFM use.[2] Our lower frequency is likely attributed to BWH's 'relaxed' formulary and our sample was composed of NFMs previously approved by pharmacist for use, hence also decreasing the number of inappropriate alert overrides.

The literature on formulary CDS is scarce. Our secondary findings provide important perspective on the better design of these informatic tools for automated formulary management. First, improvement in NFM alert systems should be prioritized to focus on non-oral NFMs. Non-oral NFMs have greater formulary cost-implications than oral NFMs. Sweet et al estimated the successful conversion of non-oral NFMs to a formulary alternative saves $7.04 to $94.60 compared to $16.62 in oral NFMs.[4] Our study found non-oral NFM alert overrides more likely to be inappropriate compared to oral NFMs. Thus, optimization of automated formulary management with non-oral NFMs is more likely to ensure formulary cost-savings.

Second, it is not surprising that the provision of no reason ('blank') to NFM alerts overrides were disproportionately inappropriate. This is likely reflective of BWH's 'relaxed' formulary, but also a characteristics volunteer free-texted alert system.[16] Mandating the provision of an override reason may decrease the frequency of inappropriate NFM alert overrides.

Third, we expected NFM alerts overridden with clinical reasons (pharmacological, specialist recommendation, and therapeutic failure / intolerant to formulary alternatives) to be more likely appropriate, but was only able to demonstrate this relationship with alerts overridden with 'disease or condition' reasons. The inability to demonstrate this hypothesis with the former clinical reasons is likely due to their small numbers in our sample. Our previous study found clinical reasons were rarely entered into our alert system ***(cite AJHP study)***, which is

surprising with our sampling being composed of only approved NFM overrides. Chart review found nearly all 'blank' (45 of the 51) and 'marginal value' (28 of the 30) reasons were of clinical reasons and potentially appropriate in our post-hoc analysis **(Table 4)**. Thus, mandating the provision of any override reason is likely to increase the frequency of alerts overridden with clinical reasons, inherently decreasing the frequency of inappropriate NFM alert overrides.

Fourth, chart review found inappropriate NFM alert overrides were largely attributed to prescriber not trialing formulary alternatives prior to the NFM. This is likely due to BWH's large number of NFMs managed by a soft stop, where guidance to formulary alternatives is not provided. Listing formulary alternatives in the pop-up alerts is likely to facilitate the use and trial of formulary alternatives, hence decreasing the frequency of inappropriate NFM alert overrides. A recent study found an obtrusive, hard-stop, pop-up alert prompting formulary interchange decreased non-formulary non-adherence by 65%.[17] In addition a list of formulary alternatives that is clear, concise, and include links to additional information may further decrease the frequency of inappropriate NFM alert overrides.[11,18-20]

Limitations

Our study has a number of limitations. First, our study was retrospective and we limited our review to the information documented in the inpatient medical notes. There were three 'blank' overrides where no citation or information regarding the rationale of NFM use was found in the inpatient notes. Contrary, there were numerous incidences where 'blank' overrides were actually justified after chart review. This leads us to infer that potentially

prescribers could have discussed the rationale for NFM use with the team, specialist, or rounding pharmacist, but failed to document appropriately in the NFM alert pop-up window.

Second, our study was undertaken at a single medical center with an in-house developed COPE system and utilized appropriateness criteria specific to one institution. Thus the results may not be fully generalizable to other institutions and medication ordering system. Nevertheless, our findings provide important perspective on the design of computerized formulary management systems and formulary-based CDS, which may further ensure formulary cost-savings, quality of care, and medication safety. In addition, our study empirically applied a previously developed general appropriateness criteria; thus the presented study may serve as a model for future formulary-based CDS studies and generate more override appropriateness evaluation.

Lastly, our analysis focused on only a subset of NFM alert overrides, the most approved and highest costing NFMs. Thus, it remains unknown how our findings might have differ with the inclusion of all NFMs. Yet such study is likely infeasible due to the need to create appropriateness criteria for all NFMs. Our reasonable decision to focus on the highest cost and most approved NFMs was to identify insight that may yield the greatest improvement in the use of alerts for formulary management.

Conclusion

To our knowledge, our study is the first to empirically evaluate the appropriateness of NFM alerts overrides in the inpatient setting. Evaluating the effectiveness of these overrides is inherently evaluating NFM usage. This is a labor-intensive task and requires the creation of

appropriateness criteria for each NFM. We circumvented this issue by tailoring an empirically developed NFM alert override general appropriateness algorithm to our institution's NFM policy and use criteria and focused on the most approved and high costing NFMs. The present study conservatively estimates that one in five NFM alert overrides is inappropriately overridden and at minimum mandating an override reason for each NFM alert override and adding a list of formulary alternatives to each NFM alert may decrease the frequency of inappropriate NFM alert overrides**.**

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Reference

1. Tyler LS, Cole SW, May JR, et al. ASHP guidelines on the pharmacy and therapeutics committee and the formulary system. Am J Health Syst Pharm 2008;65:1272-83.
2. Helmons PJ, Kosterink JG, Daniels CE. Formulary compliance and pharmacy labor costs associated with systematic formulary management strategy. Am J Health Syst Pharm 2014;71:407-15.
3. Pantaleo N, Wu WK, Talan M. The evaluation of nonformulary prescribing in a community teaching hospital. P T 2000;25:25-38.
4. Sweet BV, Stevenson JG. Pharmacy costs associated with nonformulary drug requests. Am J Health Syst Pharm 2001;58:1746-52.
5. Cohen MR. ISMP Medication Error Report Analysis. Hosp Pharm 2006;41:811-5, 902.
6. Cohen MR, Smetzer JL. ISMP Medication Error Report Analysis. Hosp Pharm 2011;46:238-9, 46.
7. Cohen MR, Smetzer JL. ISMP Medication Error Report Analysis. Hosp Pharm 2012;47:328-31.
8. Pummer TL, Shalaby KM, Erush SC. Ordering off the menu: assessing compliance with a nonformulary medication policy. Ann Pharmacother 2009;43:1251-7.
9. Kuperman GJ, Bobb A, Payne TH, et al. Medication-related clinical decision support in computerized provider order entry systems: a review. J Am Med Inform Assoc 2007;14:29-40.
10. Schedlbauer A, Prasad V, Mulvaney C, et al. What evidence supports the use of computerized alerts and prompts to improve clinicians' prescribing behavior? J Am Med Inform Assoc 2009;16:531-8.
11. van der Sijs H, Aarts J, Vulto A, Berg M. Overriding of drug safety alerts in computerized physician order entry. J Am Med Inform Assoc 2006;13:138-47.
12. Teich JM, Glaser JP, Beckley RF, et al. The Brigham integrated computing system (BICS): advanced clinical systems in an academic hospital environment. Int J Med Inform 1999;54:197-208.
13. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2012;60:616-31.
14. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA 2005;294:1934-43.
15. Plet HT, Hallas J, Kjeldsen LJ. Adherence to hospital drug formularies and cost of drugs in hospitals in Denmark. Eur J Clin Pharmacol 2013;69:1837-43.
16. Chused AE, Kuperman GJ, Stetson PD. Alert override reasons: a failure to communicate. AMIA Annu Symp Proc 2008:111-5.
17. Helmons PJ, Coates CR, Kosterink JG, Daniels CE. Decision support at the point of prescribing to increase formulary adherence. Am J Health Syst Pharm 2015;72:408-13.
18. Feldstein A, Simon SR, Schneider J, et al. How to design computerized alerts to safe prescribing practices. Jt Comm J Qual Saf 2004;30:602-13.
19. Sittig DF, Krall MA, Dykstra RH, Russell A, Chin HL. A survey of factors affecting clinician acceptance of clinical decision support. BMC Med Inform Decis Mak 2006;6:6.
20. Horsky J, Schiff GD, Johnston D, Mercincavage L, Bell D, Middleton B. Interface design principles for usable decision support: a targeted review of best practices for clinical prescribing interventions. J Biomed Inform 2012;45:1202-16.